Mid-Trimester Maternal Serum AFP and hCG as Markers of Preterm and Term Adverse Pregnancy Outcomes

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Abstract

Objective: To evaluate the predictive values of mid-trimester serum alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG) for preterm and term placenta-mediated adverse pregnancy outcomes (PMAPOs).

Methods: We extracted data for nulliparous women with a singleton pregnancy without aneuploidy or lethal fetal anomalies from a prospective cohort study. Maternal serum AFP and hCG measured between 13 and 17 weeks of gestation and expressed as multiples of the median (MoM) for gestational age were compared between women who developed a PMAPO (preeclampsia, intrauterine growth restriction, fetal death) before term or at term and women who did not develop any of these complications.

Results: Among 3466 nulliparous women, maternal serum AFP and hCG levels were available in 2110 and 2125 cases, respectively. Women who developed a PMAPO before term had a higher median level of serum AFP (1.4 vs. 1.1 MoM; \( P < 0.01 \)) and hCG (1.3 vs. 1.1 MoM; \( P < 0.01 \)) than controls. A serum hCG > 2.0 MoM was associated with a higher risk of PMAPO before term (RR 4.6; CI 95% 2.3 to 9.1) but had no impact on the risk of PMAPO at term (RR 1.1; CI 95% 0.7 to 1.7). Maternal serum AFP > 2.0 MoM was also associated with a significant increase in the risk of preterm PMAPO (RR 3.9; CI 95% 1.6 to 9.8) but not term PMAPO (RR 1.2; CI 95% 0.6 to 2.3).

Conclusion: Maternal serum AFP or hCG > 2.0 MoM increases the risk of preterm PMAPO but not term PMAPO in our population. We suggest that women with elevated serum AFP or hCG should receive standard pregnancy care once they have reached 37 weeks of gestation if fetal growth is in the normal range.

Résumé

Objectif : Évaluer les coefficients de prévision propres aux taux sériques d’alphafœtoprotéine (AFP) et de gonadotrophine chorionique (hCG) constatés au deuxième trimestre pour ce qui est des issues de grossesse indésirables à médiation placentaire (IGIMP) obtenues avant le terme et à terme.

Méthodes : Nous avons tiré, d’une étude de cohorte prospective, des données concernant des femmes nullipares ayant connu une grossesse monofœtale exempte d’anéuploïdie ou d’anomalies fœtales mortelles. Nous avons comparé les taux sériques maternels d’AFP et de hCG (mesurés entre 13 et 17 semaines de gestation et exprimés sous forme de multiples de la médiane [MoM] en fonction de l’âge gestationnel) des femmes ayant connu une IGIMP (prééclampsie, retard de croissance intra-utérin, décès fœtal) avant le terme ou à terme à ceux des femmes qui n’en sont pas venues à connaître de telles complications.

Résultats : Au sein d’un groupe de 3 466 femmes nullipares, les taux sériques maternels d’AFP et d’hCG étaient connus dans 2 110 cas et 2 125 cas, respectivement. Les femmes qui ont connu une IGIMP avant le terme présentaient des valeurs de MoM pour ce qui est des taux sériques d’AFP (1,4 vs 1,1 MoM; \( P < 0,01 \)) et de hCG (1,3 vs 1,1 MoM; \( P < 0,01 \)) plus élevées que celles des femmes du groupe témoin. Bien que la constatation d’un taux sérique de hCG > 2,0 MoM ait été associée à un risque accru d’IGIMP avant le terme (RR, 4,6; IC à 95 %, 2,3 - 9,1), elle n’exerçait aucun effet sur le risque d’IGIMP à terme (RR, 1,1; IC à 95 %, 0,7 - 1,7). La constatation d’un taux sérique maternel d’AFP > 2,0 MoM a également été associée à une hausse considérable du risque d’IGIMP avant le terme (RR, 3,9; IC à 95 %, 1,6 - 9,8); le risque d’IGIMP à terme (RR, 1,2; IC à 95 %, 0,6 - 2,3) n’en était toutefois pas affecté.

Conclusion : Au sein de la population à l’étude, les taux sériques maternels d’AFP ou de hCG > 2,0 MoM ont entraîné une hausse du risque d’IGIMP avant le terme, mais n’ont pas exercé une influence sur le risque d’IGIMP à terme. Lorsque la croissance fœtale se situe dans la plage normale, les femmes qui présentent des taux sériques élevés d’AFP ou de hCG devraient recevoir des soins de grossesse standard, une fois qu’elles ont atteint 37 semaines de gestation.
INTRODUCTION

Mid-trimester maternal serum markers have been used for prenatal aneuploidy screening for more than 20 years. In the absence of aneuploidy or neural tube defect, these serum markers have also been associated with several placenta-mediated adverse pregnancy outcomes, including preeclampsia, intrauterine growth restriction, and stillbirth. The Society of Obstetricians and Gynaecologists of Canada suggests an increased frequency of placental serum alpha-fetoprotein (> 2.5 MoM) and/or human chorionic gonadotropin (> 3.0 MoM) is associated with this increased frequency of PMAPOs. The on the other hand, recent reviews and meta-analyses found that neither of these two markers used in isolation is a good predictor of adverse pregnancy outcomes.

A growing body of evidence suggests that deep placentation disorders, which have been typically associated with preeclampsia and are mainly found in the preterm forms of the disease, are also found in all “great obstetrical syndromes” including all PMAPOs, spontaneous preterm labour and preterm premature rupture of membranes. These findings are also supported by ultrasound studies showing that abnormal first trimester and mid-trimester uterine artery Doppler velocimetry is associated more with the preterm forms of preeclampsia than the term forms, and is associated more with preterm stillbirths than term. There is an increased interest in the early prediction of preterm PMAPO because of the recent evidence showing that most could potentially be prevented with the use of low-dose ASA initiated at or before 16 weeks of gestation.

We aimed to compare the predictive value of mid-trimester maternal serum hCG and AFP for preterm and term PMAPOs in our population.

METHODS

We performed a secondary analysis of a prospective cohort of 7929 pregnant women enrolled in two hospitals in Quebec City, QC, between 2005 and 2010. These women were recruited at their first prenatal visit if they were at least 18 years old and had no chronic renal disease. Each participant signed an informed consent and completed a self-administered questionnaire regarding sociodemographic and biomedical information. After delivery, a research nurse reviewed all medical records to collect delivery data, and any cases with suspected PMAPO, including all cases of gestational hypertension of pregnancy, were reviewed by a physician blinded to the AFP and hCG results to confirm the presence or absence of PMAPO. Maternal serum AFP and hCG levels, expressed as multiples of the median (adjusted for gestational age) and collected between 13 and 17 weeks of gestation as part of the provincial Down syndrome screening program, were obtained from the hospitals’ biochemical laboratory records. Only nulliparous women with singleton pregnancies were included in our analyses. We used nulliparous women only to limit the potential bias of prophylactic measures used in women with a PMAPO in a prior pregnancy. Women with a fetus with aneuploidy or lethal anomalies or with a pregnancy that did not exceed 20 weeks of gestation were excluded.

Our outcomes of interest included any of these three PMAPOs: preeclampsia, IUGR (birth weight less than the 10th percentile for gestational age), and intrauterine fetal death. Preeclampsia was diagnosed on the basis of gestational hypertension (diastolic blood pressure of ≥ 90 mmHg based on the average of at least two measurements taken 4 hours apart after 20 weeks of gestation) combined with proteinuria (≥ 0.3 g/day in a 24-hour urine collection or ≥ 2+ on a dipstick). In women with pre-existing hypertension, preeclampsia was defined as resistant hypertension combined with new or worsening proteinuria or at least one adverse condition of pregnancy.

A Canadian growth curve chart was used to establish the percentile of every birth weight.

Based on the presence or absence of PMAPO and gestational age at delivery, our study population was stratified into four groups:

1. preterm delivery associated with PMAPO;
2. term delivery associated with PMAPO;
3. preterm delivery without PMAPO;
4. term delivery without PMAPO (controls).

Median MoM of maternal mid-trimester serum AFP and hCG in each of the first three groups were compared to the control group using the Mann-Whitney test. We then evaluated the proportion of AFP levels > 2.5 MoM, > 2.5 MoM, > 3.0 MoM, and < 0.5 MoM, as well as hCG levels > 2.0 MoM, > 2.5 MoM, > 3.0 MoM, and < 0.5 MoM between the groups using chi-squared test. All analyses were performed using SPSS v.22.0 software (IBM Inc., Armonk, NY) and a P value < 0.05 was considered significant.
The Ethics and Scientific Committee of the CHU de Québec provided ethics approval for the project.

RESULTS

Of 7929 women, 3466 nulliparous women were eligible for the study, including 2110 (60.9%) who had an available result for serum AFP and 2125 (61.3%) for serum hCG. Among those with available serum AFP, 208 (9.9%) developed a PMAPO (including 147 [7.0%] with IUGR, 56 [2.7%] with preeclampsia, and 5 [0.2%] intrauterine fetal deaths); 30 delivered before term and 178 at term. The clinical characteristics of each group are shown in Table 1.

We observed that mid-trimester serum AFP and hCG were higher in women who developed a preterm PMAPO but not a term PMAPO, compared to controls (Table 2). In addition, we observed that serum AFP was also higher in women who delivered before term without one of our three PMAPOs of interest. Using a specific cut-off, serum AFP > 2.0 MoM was associated with a higher risk of preterm PMAPO and preterm birth without PMAPO. Serum hCG > 2.0 MoM was also associated with preterm PMAPO with a P value < 0.01 (Table 2). A serum AFP or hCG < 0.5 MoM was not associated with

Table 1. Characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Term with PMAPO</th>
<th>P</th>
<th>Preterm with PMAPO</th>
<th>P</th>
<th>Preterm without PMAPO</th>
<th>P</th>
<th>Term without PMAPO (Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, years</td>
<td>28.2 (25.6 to 30.9)</td>
<td>NS</td>
<td>28.8 (26.0 to 31.7)</td>
<td>NS</td>
<td>28.1 (25.7 to 30.9)</td>
<td>NS</td>
<td>27.6 (25.2 to 30.5)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.4 (20.4 to 25.7)</td>
<td>NS</td>
<td>22.9 (20.2 to 27.2)</td>
<td>NS</td>
<td>22.7 (20.2 to 25.8)</td>
<td>NS</td>
<td>22.5 (20.4 to 25.9)</td>
</tr>
<tr>
<td>GA at entry, weeks</td>
<td>15.0 (13.7 to 15.6)</td>
<td>NS</td>
<td>15.1 (13.4 to 15.6)</td>
<td>NS</td>
<td>15.0 (14.1 to 15.7)</td>
<td>NS</td>
<td>15.0 (14.3 to 15.6)</td>
</tr>
<tr>
<td>GA at delivery, weeks</td>
<td>39.4 (38.6 to 40.4)</td>
<td>&lt; 0.01</td>
<td>35.6 (32.3 to 36.6)</td>
<td>&lt; 0.01</td>
<td>35.4 (33.6 to 36.4)</td>
<td>&lt; 0.01</td>
<td>39.9 (39.0 to 40.6)</td>
</tr>
<tr>
<td>Birth weight, grams</td>
<td>2782 (2600 to 2962)</td>
<td>&lt; 0.01</td>
<td>2045 (1443 to 2485)</td>
<td>&lt; 0.01</td>
<td>2542 (2006 to 2865)</td>
<td>&lt; 0.01</td>
<td>3435 (3200 to 3710)</td>
</tr>
<tr>
<td>Placental weight, grams</td>
<td>391 (345 to 455)</td>
<td>&lt; 0.01</td>
<td>322 (235 to 432)</td>
<td>&lt; 0.01</td>
<td>417 (321 to 487)</td>
<td>&lt; 0.01</td>
<td>480 (422 to 550)</td>
</tr>
</tbody>
</table>

Data are reported as median (interquartile range)

GA: gestational age; NS: not significant

Table 2. Levels of mid-trimester maternal serum AFP and hCG in the study groups

<table>
<thead>
<tr>
<th></th>
<th>Term PMAPO</th>
<th>P</th>
<th>Preterm PMAPO</th>
<th>P</th>
<th>Preterm without PMAPO</th>
<th>P</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP MoM*</td>
<td>1.1 (0.9 to 1.5)</td>
<td>NS</td>
<td>1.4 (0.9 to 1.6)</td>
<td>&lt; 0.01</td>
<td>1.2 (1.0 to 1.5)</td>
<td>&lt; 0.01</td>
<td>1.1 (0.8 to 1.3)</td>
</tr>
<tr>
<td>hCG MoM*</td>
<td>1.1 (0.8 to 1.6)</td>
<td>NS</td>
<td>1.3 (0.9 to 2.3)</td>
<td>&lt; 0.01</td>
<td>1.0 (0.8 to 1.5)</td>
<td>NS</td>
<td>1.1 (0.8 to 1.5)</td>
</tr>
<tr>
<td>AFP &lt; 0.5 MoM</td>
<td>3/183 (1.6%)</td>
<td>NS</td>
<td>0</td>
<td>&lt; 0.01</td>
<td>1/113 (12.4%)</td>
<td>NS</td>
<td>20/1798 (1.1%)</td>
</tr>
<tr>
<td>AFP &gt; 2.0 MoM</td>
<td>9/183 (4.9%)</td>
<td>NS</td>
<td>5/35 (14.3%)</td>
<td>&lt; 0.01</td>
<td>14/113 (12.4%)</td>
<td>&lt; 0.01</td>
<td>59/1798 (3.3%)</td>
</tr>
<tr>
<td>AFP &gt; 3.0 MoM</td>
<td>0</td>
<td>NS</td>
<td>1/35 (2.9%)</td>
<td>NS</td>
<td>5/113 (4.4%)</td>
<td>&lt; 0.01</td>
<td>4/1798 (0.2%)</td>
</tr>
<tr>
<td>hCG &lt; 0.5 MoM</td>
<td>10/185 (5.4%)</td>
<td>NS</td>
<td>0</td>
<td>NS</td>
<td>4/111 (3.6%)</td>
<td>NS</td>
<td>63/1813 (3.5%)</td>
</tr>
<tr>
<td>hCG &gt; 2.0 MoM</td>
<td>21/185 (11.4%)</td>
<td>NS</td>
<td>12/35 (34.3%)</td>
<td>&lt; 0.01</td>
<td>10/111 (9.0%)</td>
<td>NS</td>
<td>175/1813 (9.7%)</td>
</tr>
<tr>
<td>hCG &gt; 3.0 MoM</td>
<td>6/185 (3.2%)</td>
<td>NS</td>
<td>3/35 (8.6%)</td>
<td>0.01</td>
<td>2/111 (1.8%)</td>
<td>NS</td>
<td>24/1813 (1.3%)</td>
</tr>
</tbody>
</table>

*Median (interquartile range)

NS: not significant
any of our adverse pregnancy outcomes. In Table 3, the relative risks, the sensitivity and specificity, as well as the positive and negative predictive values of serum AFP and hCG > 2.0 MoM for each individual outcome are shown. Of note, serum AFP and hCG > 2.0 MoM were not associated with any of the adverse outcomes at term. Finally, we observed no difference in the rates of women reaching 41 completed weeks of pregnancy between women with AFP > 2.0 MoM compared to ≤ 2.0 MoM (12.5% vs. 13.3%, not significant), and between women with hCG > 2.0 MoM compared to ≤ 2.0 MoM (12.7% vs. 13.1%, not significant).

**DISCUSSION**

We observed that an elevated maternal serum AFP or hCG in early mid-trimester is associated with an increased risk of preterm but not term PMAPO. Our finding is in agreement with previous studies showing that maternal second trimester serum analytes are better predictors of early-onset rather than late-onset preeclampsia. It is believed that early placental dysfunction, which influences maternal serum AFP and hCG, can lead to placental hypoperfusion and a maternal endothelial reaction that can result in fetal growth restriction, preeclampsia, and even fetal death. Numerous studies suggested that the term and preterm forms of preeclampsia are different with regard to maternal characteristics and placental pathology.

Our study is limited by the low incidence of preeclampsia (2.7%) in our population, which was predominantly composed of healthy Caucasian women, and by the fact that approximately two thirds of the population participated in the provincial maternal serum screening program. On the other hand, our study included only nulliparous women with singleton pregnancies; previous studies either have not considered parity or have included both nulliparous and multiparous women and evaluated parity as a confounding variable. Parity is associated with the risk of PMAPO, and such risk can be modified by the use of prophylactic measures such as low-dose ASA or low-molecular weight heparin in women with a previous history of preeclampsia or PMAPO.
A further strength of our study is the consideration of gestational age at birth. Indeed, most studies have evaluated the overall rate of PMAPO and only a few have provided separate data for this criterion.7–10 Finally, it could be suggested that the incidence of term PMAPOs might have been reduced by interventions (e.g., fetal monitoring, labour induction) in women with abnormal serum markers. While we cannot confirm that this was not the case, it was not common practice to intervene, and there was no such policy in our centre before 2010. Moreover, we believe that such interventions would have reduced the incidence of women reaching 41 completed weeks of gestation, which was not the case.

The SOGC recommends that an obstetrician should be consulted in order to establish a specific fetal/maternal surveillance plan for women identified to be at increased risk of obstetrical complications associated with abnormal maternal serum markers.2 Unfortunately, there is a lack of evidence supporting any specific surveillance protocol for these women.2 However, a recent randomized trial demonstrated that low-dose ASA begun at 15 to 18 weeks’ gestation was associated with a reduction in the incidence of adverse pregnancy outcomes and delivery before 34 weeks’ gestation in women with an elevated serum AFP.21 This finding is in agreement with a previous publication showing that low-dose ASA initiated before 16 weeks was associated with a reduction in rates of all preterm PMAPOs in high-risk women.13 Therefore, measurement of mid-trimester AFP and hCG levels should probably be performed as early as possible (at 14 to 15 weeks’ gestation) in order to consider the initiation of low-dose ASA therapy. However, it remains unclear whether or not such an approach would be reproducible in our population, because the positive predictive value of an elevated serum AFP remains quite low independent of the selected pregnancy outcome (Table 3). Most likely, we would need to combine or to focus on other biomarkers in order to reach sufficient sensitivity and specificity before using such markers for the prediction and prevention of PMAPOs. Toal et al. observed that assessment of placental function using either morphology or uterine artery Doppler velocimetry in mid-trimester identifies a subset at increased risk of PMAPO in women with elevated serum AFP.22 Many research groups, including ours, observed that a combination of early biomarkers, including BMI, mean arterial blood pressure, and placental growth factor (among others) could lead to a detection rate of 60% to 95% of early-onset preeclampsia, with a 5% to 10% false-positive rate.23–26 On the other hand, our results also suggest that a pregnant woman with elevated mid-trimester AFP or hCG levels is not at increased risk of term PMAPOs compared to women with normal AFP and hCG levels. Therefore, there is no support for additional monitoring or early delivery in those pregnancies, based on these results. We believe that those women should have a third-trimester ultrasound assessment for fetal growth, and should then have standard follow-up after 37 weeks.

CONCLUSION

Elevated mid-trimester maternal serum AFP or hCG (> 2 MoM) is associated with an increased risk of preterm PMAPOs in nulliparous women with a singleton pregnancy, but has no apparent effect on pregnancy outcomes after 37 weeks. Low-dose ASA therapy beginning early in the second trimester could be considered in these women. How to manage such pregnancies otherwise before 37 weeks of gestation remains to be clarified. In the presence of normal fetal growth, women with unexplained elevated second trimester AFP and/or hCG levels should have standard pregnancy management once they have reached 37 weeks of gestation.

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